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EXAMINER	
ZAREK, PAUL E	

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1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,071	SANTORO, MARIA GABRIELLA	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-78* is/are pending in the application.

4a) Of the above claim(s) *54-64,67,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65,66,68-70 and 73-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 65, 66, 68-70, and 73-75 have been amended and Claims 77 and 78 have been cancelled by the Applicant in correspondence filed on 11/24/2008. Claims 54-78 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election with traverse of Group IV, drawn to a pharmaceutical composition comprising indomethacin in combination with other compounds in the reply filed on 11/24/2008 is acknowledged. The traversal is on the ground(s) that Bourinbaiar and Lee-Huang does not disclose the special technical feature of the instant claims, and that the different groups relate to overlapping subject matter such that an art search for one compound would necessarily overlap with that of another. This is not found persuasive because Applicant has not disclosed why the art applied to break unity of invention misapplied. "The expression special technical features is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art." (MPEP § 1893.03(c)) Bourinbaiar and Lee-Huang clearly teach a composition comprising indomethacin and the antiviral drug MAP30 (abstract, Figure 1, lower left panel). Therefore, Claim 65 does not define a contribution novel over the prior art. Applicant further elected "metals and corresponding salts and derivatives" as the elected species of "second compound" of the composition with traverse. The reasons for traverse and Examiner's response to said traverse are stated above.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 65, 66, 68-70, and 73-78 read upon the elected species. Claims 54-64 are withdrawn as being drawn to a nonelected invention. Claims 67, 71, and 72 are withdrawn as being drawn to a nonelected species.

Priority

4. Applicant's claim for the benefit of a prior-filed international application PCT/EP04/51773 (filed on 08/11/2004) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The effective filing date of the instant application is 08/11/2004.

5. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) of Italian application RM2003A000394 (filed on 08/12/2003). The foreign priority date of the instant application is 08/12/2003.

Information Disclosure Statement

The information disclosure statement filed 02/13/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. A line has been drawn through them.

Claim Objections

6. Claim 65 is objected to because of the following informalities: Claim 65 recites the limitation "INDO." This is unclear as "INDO" is not definied in the claims. Applicant is advised to spell out "indomethacin" at first use, after which "INDO" would be acceptable.

7. Claim 75 is objected to because of the following informalities: Claim 75 recites the limitation "BBB." This is unclear as "BBB" is not defined in the claims. Applicant is advised to spell out "blood-brain barrier" at first use, after which "BBB" would be acceptable. Also, Claim 75 is not written in an appropriate form of a claim. "[T]he present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim," (MPEP § 608.01(m)). As written, Claim 75 is not the object of a sentence as the wherein clause is not grammatically correct. The clause requires a verb. Applicant can overcome this objection by inserting "is" after "INDO" on line 2 or by deleting "that" after "carrier." Appropriate correction is required.

Claim Rejections - 35 USC § 112 (1st paragraph)

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 76 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 76 of the instant application is drawn to a pharmaceutical composition of Claim 65 further comprising a pharmaceutically acceptable vector. Common meaning of vector in the biotechnology arts includes viruses, bacteriophages, and liposomes. There is no written support in the specification for a vector, nor a definition of what would be construed as a pharmaceutically acceptable vector. Therefore, one of ordinary skill in the art would not reasonably conclude that Applicant was in possession of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 112 (2nd paragraph)

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 65, 66, 68-70, and 73-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejected claims recite the limitation of indomethacin or "derivatives thereof." Applicant has defined "derivative" as "synthesizable by the expert in the field." (pg 3, lines 2-3). Applicant has provided no structure or guidance in the specification to

demonstrate what is meant by derivative. The term is so broad as to include almost an infinite number of compounds, including CO_2, which would be the product if a skilled artisan "derivatized" indomethacin by burning it. Therefore, the rejected claims are indefinite because the metes and bounds of this limitation are unclear.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 65, 66, 68, 73, 74, and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Regtop and Biffin (US Patent No. 5,466,824, 1995).

14. Claim 65 of the instant application is drawn to a pharmaceutical composition comprising indomethacin and/or salts and/or derivatives thereof in combination with a therapeutically effective amount of a second compound, such as an interferon, metal, prostanoids, antiviral drugs, or mixtures. Applicant elected metals as the species of this second agent. Claims 66 and 68 limit the metals and metal salts. Claim 73 limits the composition to further include pharmaceutically acceptable carriers. Claim 74 limits the dosage form for specific routes of administration. Claim 77 is drawn to a pharmaceutical composition comprising indomethacin and at least one metal, salt, and/or derivative.

15. Regtop and Biffin teach an indomethacin composition with divalent metals, preferably zinc (col 4, lines 19-20). Regtop and Biffin further teach a pharmaceutical composition that can

be administered orally, parenterally, rectally, or topically and includes pharmaceutically acceptable carriers, diluents, and excipients (col 3, lines 33-40). Therefore, Regtop and Biffin anticipate all the limitations of the rejected claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regtop and Biffin (above) in view of Berge, et al. (Journal of Pharmaceutical Sciences, 1977).

18. Claim 69 further limits the composition of Claim 65 to comprise metal salt limiting the anion (i.e. chloride, sulfate, lactate, etc). Claim 70 further limits the composition of Claim 65 to comprise specific zinc salts (i.e. $ZnCl_2$, $ZnSO_4$, etc.).

19. Regtop and Biffin teach an indomethacin composition comprising indomethacin and a metal salt. The metal is preferably Zn (col 4, lines 19-20). The salt is generically taught, indicating virtually any acceptable salt, and the only disclosed salt is acetate (col 3, lines 2-4). Regtop and Biffin do not teach an indomethacin composition comprising a salt containing the anion of Claim 69, or the specific Zn salts of Claim 70.

20. Berge, et al., teach a variety of FDA-approved anions, including acetate (the species taught by Regtop and Biffin) as well as chloride, sulfate, lactate, citrate, maleate, salicylate, fumarate, and succinate. Note that many of the salts of Claim 69 are commonly used in

pharmaceutical formulations. For example, chloride was used in 4.17% of all drugs through 1974, and sulfate in 7.46%. This indicates that the salts of Claims 69 and 70 would have been known on one of ordinary skill in the art at the time the invention was made. Therefore, it would have been *prima facie* obvious to use these salts in the formulation of a pharmaceutical composition comprising indomethacin and a metal salt.

21. Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Regtop and Biffin (above) in view of Wilkinson (Goodman & Gilman's The Pharmaceutical Basis of Therapeutics 10th ed., Chapter 1: Pharmacokinetics, 2001).

22. Claim 75 of the instant application is drawn to an indomethacin composition further comprising a carrier wherein the composition can cross the blood-brain barrier.

23. Regtop and Biffin teach an indomethacin and metal salt composition but does not teach the ability of the composition to cross the blood-brain barrier.

24. Wilkinson teaches that the blood-brain barrier restricts entry of drugs to the CNS due to the physiology of the brain capillary endothelial cells. Wilkinson provides guidance on how to overcome the blood-brain barrier. To wit: "the lipid solubility of the nonionized and unbound species of the drug is an important determinant of its uptake by the brain: the more lipophilic it is, the more likely it is to cross the blood-brain barrier." (pg 10, col 2, lines 9-12) To treat a viral infection within the CNS, the ordinarily skill artisan would have to overcome the blood-brain barrier. Many drugs have been developed that can cross the blood-brain barrier, and one of ordinary skill in the art would know which carriers to use that would follow the guidelines of Wilkinson. The skilled artisan would be motivated to create antiviral compositions that cross the blood-brain barrier because there viruses that can infect/reside in the CNS, such as HIV and

coxsackieviruses. Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to add a carrier which would allow for the crossing of the blood-brain barrier to the indomethacin/metal salt composition taught by Regtop and Biffin to

25. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Regtop and Biffin (above) in view of Engler, et al. (US Patent No. 6,165,779, 2000).

26. Claim 76 is drawn to a composition of indomethecin and a metal salt further comprising a vector.

27. Regtop and Biffin teach an indomethacin and metal salt composition but does not teach a composition to further comprise a vector.

28. Engler, et al., teach a gene delivery system comprising of lipid-encapsulated DNA, which is reasonably interpreted to be a vector. Engler, et al., further teach various compounds, such as indomethacin, which are known "delivery-enhancing agents." (col 4, lines 5-6). Vectors are advantageous in drug delivery because they allow for targeted delivery of the drug to a specific site or cell-type within the body. Since indomethacin is known to enhance the delivery of the vector, it would have been *prima facie* obvious to include indomethacin in a composition further comprising a vector.

29. Claim 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Regtop and Biffin (above) in view of Taylor, et al. (US Patent No. 6,303,295, 2001).

30. Claim 78 is drawn to a composition comprising indomethacin and a metal selected from the group of gold, selenium, or bismuth, and/or corresponding salts and/or derivatives.

31. Regtop and Biffin teach an indomethacin and metal salt composition but does not teach a composition to comprise specifically gold, selenium, or bismuth.

32. Taylor, et al., teaches the importance of dietary selenium for proper immune function. "Se supplementation increases immunoglobin G synthesis, increased chemotactic responses in neutrophils, and enhancement of both T cell cytotoxicity and proliferation in response to mitogens and antigens. Impairment of these immune functions can include reduced T cell counts, including reduced CD4+ T cell counts, and impaired lymphocyte proliferation and responsiveness." (col 1, lines 50-57) One of ordinary skill in the art would recognize that Se has beneficial effects on enhancing the T cell response, which is imperative in fighting off viral infections. Since it is known that indomethacin and selenium possess antiviral faculties, it would have been obvious to combine them in a single formulation. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (MPEP § 2144.06(I).

Conclusion

33. Claims 65, 66, 68-70, and 73-78 are rejected.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/
Primary Examiner, Art Unit 1625